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Award Number: DAMD17-99-1-9397

TITLE: Impact of Axillary Dissection on Clinical Outcomes of
Breast Cancer Surgery

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REPORT DATE: June 2000

TYPE OF REPORT: Annual Summary

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
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DTIC QUALITY INSPECTED 4

20001005 063

REPORT DOCUMENTATION PAGE			Form Approved OMB No. 074-0188	
Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing this collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to Washington Headquarters Services, Directorate for Information Operations and Reports, 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302, and to the Office of Management and Budget, Paperwork Reduction Project (0704-0188), Washington, DC 20503				
1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE June 2000	3. REPORT TYPE AND DATES COVERED Annual Summary (1 Jun 99 - 30 Jun 00)		
4. TITLE AND SUBTITLE Impact of Axillary Dissection on Clinical Outcomes of Breast Cancer Surgery		5. FUNDING NUMBERS DAMD17-99-1-9397		
6. AUTHOR(S) Xianglin Du, Ph.D.				
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) The University of Texas Medical Branch at Galveston Galveston, Texas 77555-0136 E-MAIL: xdu@utmb.edu		8. PERFORMING ORGANIZATION REPORT NUMBER		
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012		10. SPONSORING / MONITORING AGENCY REPORT NUMBER		
11. SUPPLEMENTARY NOTES				
12a. DISTRIBUTION / AVAILABILITY STATEMENT Approved for public release; distribution unlimited			12b. DISTRIBUTION CODE	
13. ABSTRACT (Maximum 200 Words) We studied 26,290 women with early-stage breast cancer aged ≥ 25 in 1983-1993 who received BCS, using data from the Surveillance, Epidemiology and End Results Program and Medicare. Twenty seven percent of women aged ≥ 25 receiving BCS did not receive axillary dissection, most of whom (74%) were age ≥ 65 . Women receiving BCS with axillary dissection had lower 7-year breast cancer-specific mortality than did those without dissection (hazard ratio=0.53, 95% confidence interval: 0.44-0.63). We found an interaction between receipt of axillary dissection and radiotherapy on survival of older women after BCS. Women who received either axillary dissection or radiotherapy experienced similar survivals to those who received both axillary dissection and radiation, while women who received neither treatment experienced poorer survival (hazard ratio=1.76, 1.23-2.52), after controlling for demographics, tumor size and comorbidity. In conclusion, the combination of no axillary dissection plus no radiation after BCS is associated with an unacceptably high level of deaths from breast cancer. The lack of improvement in the past two decades in survival of older women with breast cancer may be explained in part by the increasing use of treatments that do not address potential tumor in axillary nodes.				
14. SUBJECT TERMS Breast Cancer			15. NUMBER OF PAGES 11	
			16. PRICE CODE	
17. SECURITY CLASSIFICATION OF REPORT Unclassified	18. SECURITY CLASSIFICATION OF THIS PAGE Unclassified	19. SECURITY CLASSIFICATION OF ABSTRACT Unclassified	20. LIMITATION OF ABSTRACT Unlimited	

FOREWORD

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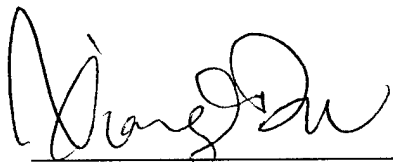
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Introduction

Increasing numbers of older women with breast cancer are receiving breast-conserving surgery (BCS) without axillary dissection. While such an approach appears efficacious in randomized controlled trials, there is concern that it contributes to higher breast cancer mortality in the community. Our aim was to determine whether failure to perform axillary dissection is associated with decreased survival in women with early-stage breast cancer. We studied 26,290 women with early-stage breast cancer aged ≥ 25 in 1983-1993 who received BCS, using data from the Surveillance, Epidemiology and End Results Program and Medicare.

Body

Key Research Accomplishments

The findings of this study so far can be summarized as follows. First, substantial numbers of older women receiving breast-conserving surgery do not receive axillary dissection.^{1,2} Second, of those women not receiving axillary dissection, most also do not receive either adjuvant radiation therapy or chemotherapy.³ In other words, they receive no therapy directed at occult cancer in the axillary nodes. The percentage of older women who receive no therapy to their axillary nodes has been steadily increasing over the past decade.^{1,4} Third, patients receiving breast-conserving surgery without axillary dissection experience significantly worse survivals than those who do, after controlling for other factors known to affect survival. Finally, there is an interaction between receipt of axillary dissection and radiation therapy on survival, such that women who receive either axillary dissection or radiation therapy experience similar survivals to those who receive both axillary dissection and radiation, while women who receive neither treatment experience substantially poorer survivals.

Reportable outcomes

Table 1 presents the percentages of women receiving breast-conserving surgery (BCS) with or without axillary dissection by patient and tumor characteristics. Overall, 27% of all women with early stage breast cancer who underwent BCS did not receive axillary dissection as part of initial surgical treatment. Older women, unmarried women and those with very small (<0.5 cm) or very large tumors (≥ 4.0 cm) were less likely to receive axillary dissection. The data on the percentages receiving axillary dissection by stage are misleading, because the major means of distinguishing regional from local stage is by axillary dissection. Thus there is a misclassification bias of underreporting regional stage tumor in women without axillary dissection. Because of this, in the survival analyses we control for tumor size rather than stage.

As discussed in the Introduction, axillary dissection may be less important if patients not receiving axillary dissection receive adjuvant radiation therapy or chemotherapy.^{5,6} We investigated this issue in women aged 65 and over and diagnosed with early stage breast cancer between 1991 and 1993 using the SEER-Medicare linked data, which provides information on radiation therapy, chemotherapy, and comorbid conditions.⁷ Table 2 presents the percentage of women receiving radiation and chemotherapy as a function of receipt of axillary node dissection.

Of women receiving BCS without axillary dissection, nearly two-thirds (62%) also did not receive radiation therapy. The great majority of these older women (98%) did not receive chemotherapy. Women not receiving axillary dissection actually had a lower chance of receiving radiation or chemotherapy than those receiving axillary dissection.

Table 3 presents the interaction between axillary dissection and receipt of radiation therapy on mortality of women aged 65 and older with early stage breast cancer. Women receiving neither axillary dissection nor radiotherapy were at a significantly higher risk for death, compared to those who received both axillary dissection and radiation therapy. Women receiving either radiation alone without axillary dissection, or axillary dissection without radiation were not at significantly higher risk for death, after adjusting for patient and tumor characteristics.

Conclusions

In conclusion to date, the combination of no axillary dissection plus no radiation after BCS is associated with an unacceptably high level of deaths from breast cancer. The lack of improvement in the past two decades in survival of older women with breast cancer may be explained in part by the increasing use of treatments that do not address potential tumor in axillary nodes. Further research will be performed to look at social economic factors in relation to the effect of axillary node dissection on clinical outcomes.

From the performance of this study, a great deal has been learnt about using the large databases such as Medicare claims for research. Considerable experience has been gained in using Medicare data to explore comorbidity status and treatment procedures, and in performing survival analyses.

References

1. Du XL, Freeman JL, Goodwin JS. The declining use of axillary dissection in patients with early stage breast cancer. *Breast Cancer Res Treat* 1999;53:137-144.
2. Bland KI, Scott-Conner CE, Menck H, Winchester DP. Axillary dissection in breast-conserving surgery for stage I and II breast cancer: a National Cancer Data Base study of patterns of omission and implications for survival. *J Am Coll Surg* 1999;188:586-95.
3. Early Breast Cancer Trialists' Collaborative Group. Effects of radiotherapy and surgery in early breast cancer. An overview of the randomized trials. *N Eng J Med* 1995;333:1444-55.
4. Du XL, Freeman JL, Freeman DH, Syblik DA, Goodwin JS. Temporal and regional variation in the use of breast conserving surgery and radiotherapy for older women with early stage breast cancer from 1983 to 1995. *J Gerontol (Med Sci)* 1999;54A:474-8.
5. Ruffin WK, Stacey-Clear A, Younger J, Hoover HC, Jr. Rationale for routine axillary dissection in carcinoma of the breast. *J Am College Surg* 1995;180:245-51.

6. Recht A, Houlihan MJ. Axillary lymph nodes and breast cancer: a review. *Cancer* 1995;76:1491-512.
7. Du XL, Freeman JL, Goodwin JS. Information on radiation treatment in patients with breast cancer: the advantages of the linked Medicare and SEER data. *J Clin Epidemiol* 1999;52:463-70.

Appendix

Appendix 1. Tables 1-3.

Table 1. Receipt of axillary dissection by women with breast cancer who received breast conserving surgery (BCS) between 1988 and 1993 in 9 SEER areas, by patient and tumor characteristics

Patient and tumor characteristics	Number (%) of women receiving BCS* without axillary dissection	Number (%) of women receiving BCS* with axillary dissection	Total
Age (years)			
25-54	931 (10.2)	8173 (89.8)	9104
55-64	835 (15.2)	4674 (84.8)	5509
65-74	1604 (26.0)	4573 (74.0)	6177
75+	3421 (62.2)	2079 (37.8)	5500
Race			
White	6021 (26.0)	17145 (74.0)	23166
Black	463 (26.1)	1313 (73.9)	1776
Other	252 (20.9)	955 (79.1)	1207
Unknown	55 (39.0)	86 (61.0)	141
Marital status			
Married	2588 (17.4)	12276 (82.6)	14864
Unmarried	3866 (36.0)	6876 (64.0)	10742
Unknown	337 (49.3)	347 (50.7)	684
Cancer stage			
Stage I	5143 (28.7)	12750 (71.3)	17893
Stage IIA	1442 (22.4)	4998 (77.6)	6440
Stage IIB	190 (10.8)	1564 (89.2)	1754
Stage II,NOS †	16 (7.9)	187 (92.1)	203
Tumor size (cm)			
<0.5	472 (38.9)	743 (61.1)	1225
0.5-<1.0	1294 (25.0)	3883 (75.0)	5177
1.0-<2.0	2857 (23.9)	9089 (76.1)	11946
2.0-<3.0	1362 (25.2)	4053 (74.8)	5415
3.0-<4.0	466 (30.4)	1066 (69.6)	1532
4.0+	324 (40.4)	478 (59.6)	802
Unknown size	16 (7.9)	187 (92.1)	203
Total	6791 (25.8)	19499 (74.2)	26290

* BCS denotes breast-conserving surgery.

† NOS - not specified.

Table 2. Receipt of radiation therapy and chemotherapy in women aged 65 and older who underwent breast conserving surgery in 1991 through 1993, with or without axillary node dissection*

Surgical treatment categories	Number of patients	Number (%) of women receiving radiation therapy †	Number (%) of women receiving chemotherapy ‡
breast conserving surgery without axillary dissection	2215	853 (38.5)	52 (2.4)
breast conserving surgery with axillary dissection	2974	2673 (85.9)	163 (5.2)

* For women with early stage (local or regional) breast cancer diagnosed between 1991 and 1993 from the SEER-Medicare linked database.

† Radiation therapy was defined if SEER data indicated so or if there were Medicare claims for radiation therapy within 4 months after diagnosis of breast cancer.

‡ Chemotherapy was defined if patients had at least one Medicare claim for chemotherapy within 12 months after diagnosis.

Table 3. Interaction between receipt of axillary dissection and radiation therapy on breast cancer survival in women aged 65 and older with early stage breast cancer, 1991-1993

Variables	Number of patients (n=5328)	Hazard ratio for 3-year breast cancer specific mortality (95% CI) †
Patients receiving BCS, by receipt of axillary dissection (Ax) and radiation (XRT)*		
No Ax + no XRT	1362	1.76 (1.24-2.49)
No Ax + XRT	853	1.11 (0.74-1.68)
Ax + no XRT	440	1.00 (0.59-1.70)
Ax + XRT	2673	1.00
Other key risk factors in the model		
Age (years)		
65-69	1287	1.00
70-74	1415	1.03 (0.69-1.53)
75-79	1189	1.02 (0.67-1.54)
80+	1437	1.15 (0.76-1.74)
Tumor size (cm)		
<0.5	264	1.00
0.5-<1.0	1252	1.11 (0.42-2.93)
1.0-<2.0	2419	2.07 (0.84-5.12)
2.0-<3.0	968	3.51 (1.40-8.77)
3.0-<4.0	255	6.76 (2.62-17.44)
4.0+	138	5.50 (2.00-15.12)
Unknown size	32	2.52 (0.89-7.09)
Comorbidity index scores ‡		
No Medicare claims	344	0.82 (0.44-1.54)
0	3616	1.00
1	637	1.53 (1.06-2.22)
2	323	1.76 (1.11-2.79)
3+	408	2.05 (1.37-3.05)

* BCS (breast-conserving surgery), No Ax (no axillary dissection); no XRT (no radiation therapy); Ax (axillary dissection); XRT (radiation therapy).

† Hazard ratios (95% confidence interval), adjusted for the variables listed in the table and also adjusted for marital status (married, unmarried and unknown), race (white, black, and other), and 9 SEER areas.

‡ Comorbidity was assessed by a validated algorithm^{29,30} using Medicare claims.

Appendix 2. Abstract.

Abstract was presented at the Society for Epidemiologic Research annual meeting, Seattle, WA, June 15-17, 2000; and published in the Am J Epidemiol 2000;151(suppl):S64.

S64 SER Abstracts

THE EFFECT OF AXILLARY NODE DISSECTION ON SURVIVAL IN WOMEN WITH EARLY STAGE BREAST CANCER. XL Du,* JL Freeman, AB Nattinger, and JS Goodwin (University of Texas Medical Branch, Galveston, TX 77555)

Increasing numbers of older women with early stage breast cancer are receiving breast-conserving surgery (BCS) without axillary dissection. While such an approach appears efficacious in randomized controlled trials, there is concern that it contributes to higher breast cancer mortality in the community. We studied 26,290 women aged ≥ 25 in 1983-93 from the Surveillance, Epidemiology and End Results (SEER) Program and 5,328 women aged ≥ 65 in 1991-93 from SEER-Medicare linked data, who had an early stage breast cancer and received BCS. Overall, 27% of women aged ≥ 25 receiving BCS did not receive axillary dissection, most of whom (74%) were age ≥ 65 . Women receiving BCS with axillary dissection had lower 7-year breast cancer-specific mortality than did those without axillary dissection (Cox proportional hazard ratio=0.53, 95% confidence interval: 0.44-0.63). Women not receiving axillary dissection actually had a lower chance of receiving radiation or chemotherapy than those receiving axillary dissection. Of women receiving BCS without axillary dissection, 62% also did not receive radiation therapy and 98% did not receive chemotherapy. We found an interaction between receipt of axillary dissection and radiotherapy on survival of older women after BCS. Women who received either axillary dissection or radiotherapy experienced similar survivals to those who received both axillary dissection and radiation, while women who received neither treatment experienced poorer survival (hazard ratio=1.76, 1.23-2.52), after controlling for demographics, tumor size and comorbidity. The findings suggested that the combination of no axillary dissection plus no radiation after BCS is associated with an unacceptably high level of deaths from breast cancer. The lack of improvement in the past 2 decades in survival of older women with breast cancer may be explained in part by the increasing use of treatments that do not address potential tumor in axillary nodes.